Gastroschisis in Europe - A Case-malformed-Control Study of Medication and Maternal Illness during Pregnancy as Risk Factors

Given, Joanne E.; Loane, Maria; Garne, Ester; Nelen, Vera; Barisic, Ingeborg; Randrianaivo, Hanitra; Khoshnood, Babak; Wiesel, Awi; Rissmann, Anke; Lynch, Catherine

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Authors:

Joanne E. Given [1], Maria Loane[2], Ester Garne[3], Vera Nelen[4], Ingeborg Barisic[5], Hanitra Randrianaivo[6], Babak Khoshnood[7], Awi Wiesel[8], Anke Rissmann[9], Catherine Lynch[10], Amanda J.Neville[11], Anna Pierini[12], Marian Bakker[13], Kari Klungsoyr[14], Anna Latos Bielenska[15], Clara Cavero-Carbonell[16], Marie-Claude Addor[17], Natalya Zymak-Zakutnya[18], David Tucker[19], Helen Dolk[2].

[1] Administrative Data Research Centre Northern Ireland, Ulster University, Northern Ireland. [2] School of Nursing, Ulster University, Northern Ireland. [3] Paediatric Department, Hospital Lillebaelt, Kolding, Denmark. [4] Provinciaal Instituut voor Hygiene (PIH), Antwerp, Belgium. [5] Children's Hospital Zagreb, Medical School University of Zagreb, Croatia. [6] Registre des Malformations Congenitales de la Reunion, St Pierre, Ile de la Reunion. [7] Paris Registry of Congenital Anomalies, Maternité de Port-Royal, PARIS, France. [8] Mainz Model Birth Registry, University Children's Hospital Mainz, Germany. [9] Malformation Monitoring Centre Saxony-Anhalt, Otto-von-Guericke University Magdeburg, Germany. [10] Department of Public Health, Health Service Executive – South East, Ireland. [11] IMER Registry (Emilia Romagna Registry of Birth Defects), University of Ferrara and Azienda Ospedaliero Universitaria di Ferrara, Italy. [12] Tuscany Registry of Congenital Defects, CNR Institute of Clinical Physiology/Fondazione Toscana "Gabriele Monasterio", Pisa, Italy. [13] Eurocat Northern Netherlands, University of Groningen, the Netherlands. [14] Domain for health data and digitalization, Norwegian Institute of Public Health, Bergen, Norway and Department of Global Public Health and Primary Care, University of Bergen, Norway. [15] Polish Registry of

Congenital Malformations, Department of Medical Genetics, Poland. [16] *Rare Diseases Joint Research Unit, FISABIO-UVEG, Spain.* [17] *Medical Genetics, CHUV, Switzerland.* [18] *OMNI-Net, Khmelnytsky Regional Medical Genetic Center, Ukraine.* [19] *Congenital Anomaly Register and Information Service for Wales, Public Health Wales, United Kingdom.*

Correspondence:

Dr Joanne Given, Ulster University, Room 12L10D, Jordanstown Campus, Shore Road, Newtownabbey, BT37 0QB.

Telephone: +442890366374.

Email: je.given@ulster.ac.uk.

Fax number: +44 28 90366374.

Abstract

Background: Gastroschisis, a congenital anomaly of the abdomen, is associated with young maternal age and has increased in prevalence in many countries. Maternal illness and medication exposure are among environmental risk factors implicated in its aetiology.

Methods: A population-based case-malformed control study was conducted using data from 18 European congenital anomaly registries, with information on first trimester medication use, covering 8 million births 1995-2012. 1,577 gastroschisis cases (of which 4% stillbirths, 11% terminations of pregnancy) were compared to 153,357 non-chromosomal/monogenic controls. Literature review identified previous associations concerning maternal illness and medication exposure to be tested as signals. Logistic regression adjusted for maternal age group, registry and time period was used to evaluate associations.

Results: Comparing gastroschisis to other congenital anomalies, the data supported signals concerning maternal depression [aOR 2.52, 95% CI 1.45, 4.39], antidepressant use [aOR 2.03, 95% CI 1.22, 3.38], postnatal depression/psychosis following a previous pregnancy [aOR 8.32, 95% CI 2.56, 27.01], sexually transmitted infections [aOR 2.85, 95% CI 1.13, 7.24], topical antivirals [aOR 5.31, 95% CI 1.63, 17.33] and continuation of oral contraceptives in early pregnancy [aOR 2.17, 95% CI 1.13, 4.18]. Exploratory analyses suggested associations with a wider range of maternal infections and medications, including tonsillitis and the expectorant bromhexine.

Conclusions: While it is difficult to disentangle the effects of the medication and underlying indication, our results add to the evidence base on preventable risk factors for gastroschisis.

These risk factors may contribute to the higher risk among young mothers, and geographical and temporal variation in prevalence.

Gastroschisis in Europe– A Case-malformed Control Study of Medication and Maternal Illness During Pregnancy as Risk Factors

Introduction

Gastroschisis is a congenital anomaly where the small intestine, part of the large intestine and occasionally other abdominal organs protrude through a lateral defect in the ventral abdomen.[1,2] The majority of cases are isolated anomalies.[3] The pathogenesis of gastroschisis is uncertain but it is thought to occur between the third and eighth gestational weeks. Historically a vascular disruption mechanism was proposed but recent hypotheses focus on abnormalities in the process of body wall[4] or umbilical ring[1] development.

Young maternal age has consistently been associated with an increased risk of gastroschisis.[5,6] Links have also been found with nulliparity,[7] white, Hispanic and indigenous Australian ethnic groups,[7,8] smoking,[9] alcohol,[10] illicit drug use,[11] medication exposure,[9,12] maternal illness[13] and low pre-pregnancy body mass index.[14] None of these factors have been found to explain the geographical variation in prevalence in Europe,[5] or the increase in prevalence seen since the 1970s.[7,15]

EUROmediCAT is a population based reproductive pharmacovigilance system, based on the European Surveillance of Congenital Anomalies (EUROCAT) network, and provides an opportunity to undertake research on medication exposure and maternal illness.[16,17] This study aimed to use the EUROmediCAT database to test signals from the literature concerning first trimester medication exposure and maternal illness as risk factors for gastroschisis.

Methods

A case-malformed control study was conducted using the EUROmediCAT database. Cases of gastroschisis were compared to controls with other non-chromosomal/monogenic congenital anomalies. The case-malformed control methodology was initially proposed for birth defect epidemiology as a method of controlling for maternal recall bias.[18,19] It is used in EUROmediCAT to control for the source of exposure data and because data on non-malformed controls are not available.[20]

Study population and data

EUROCAT registries record all cases of major congenital anomalies among live births, fetal deaths ≥20 weeks' gestation and termination of pregnancy for fetal anomaly (TOPFA), in their populations using International Classification of Diseases (ICD)-9/ICD-10-British Paediatric Association (BPA) codes.[16] The EUROmediCAT database includes data, from 1995, from those EUROCAT registries that record first trimester medication exposure either directly or through linkage with healthcare databases.[21] Eighteen EUROmediCAT registries, across 14 countries 1995-2012 covering 8,096,594 births, participated in this study (Table 1).

Table 1. Total births in population, number of Gastroschisis cases, number of malfromed controls, and total prevalence of Gastroschisis per 10,000 births by EUROCAT Registry, 1995-2012

Country	Registry	Time period	Total births in population	Gastroschisis cases[a]	Malformed controls	Total prevalence of gastroschisis per 10,000 births [95% Confidence Interval]
Belgium	Antwerp	1997-2012	308,067	43	6,510	1.4 [1.0, 1.9]
Croatia	Zagreb	1995-2012	120,403	21	1,858	1.7 [1.1, 2.7]
Denmark	Odense	1995-2012	96,816	22	2,167	2.3 [1.4, 3.4]
France	Isle de Reunion	2002-2012	161,071	37	3,530	2.3 [1.6, 3.2]
France	Paris	2001-2012	319,636	51	7,608	1.6 [1.2, 2.1]
Germany	Mainz	1996-2012	55,436	33	2,246	6.0 [4.1, 8.4]

Germany	Saxony Anhalt	1995-2012	274,845	104	7,939	3.8 [3.1, 4.6]
Ireland	South East Ireland	1997-2012	108,730	14	1,657	1.3 [0.7, 2.2]
Italy	Emilia Romagna	1995-2012	595,214	52	9,923	0.9 [0.7, 1.1]
Italy	Tuscany	1995-2012	505,101	34	9,277	0.7 [0.5, 0.9]
Netherlands	Northern Netherlands	1995-2012	340,310	38	7,373	1.1 [0.8, 1.5]
Norway	Norway	2005-2010	364,160	116	9,249	3.2 [2.6, 3.8]
Poland	Poland	1999-2010	3,228,380	532	43,750	1.6 [1.5, 1.8]
Poland	Wielkopolska	1999-2010	440,096	71	10,683	1.6 [1.3, 2.0]
Spain	Valencia Region	2007-2012	314,704	37	5,939	1.2 [0.8, 1.6]

Switzerland	Vaud	1997-2012	120,397	18	3,729	1.5 [0.9, 2.4]
Ukraine	Ukraine	2005-2012	241,508	86	5,219	3.6 [2.8, 4.4]
United Kingdom	Wales	1998-2012	501,720	278	16,220	5.5 [4.9, 6.2]
Total		**1995-2012**	**8,096,594**	**1,587**[b]	**154,877**	**2.0 [1.9, 2.1]**

a Total cases = (Live births + stillbirths+ terminations of pregnancy). Excludes those with a chromosomal/monogenic syndrome

b Ten gastroschisis cases were excluded from the case-malformed control analysis as they were also recorded as having omphalocele, non-specific abdominal wall anomalies, limb-body-wall complex or body stalk anomalies.

Cases and controls

Gastroschisis cases were those with an ICD-9 with BPA extension code 75671 or ICD-10 code Q793. Malformed controls consisted of those with a diagnosis of a major congenital anomaly not including gastroschisis. Those with codes for omphalocele (ICD-9-BPA 75670 or ICD-10 code Q792), non-specific abdominal wall anomalies (ICD-9-BPA 75679), limb-body-wall complex (ICD-10 Q795) or body stalk anomalies were excluded from both cases and controls.[16] Chromosomal/monogenic conditions were excluded from cases and controls. Cases and controls were classified as isolated or potentially multiply malformed using the EUROCAT algorithm.[22]

Exposure

First trimester maternal medication exposures were mostly obtained by registries from prospectively recorded maternity records. Additional data sources included the medical records of the infant, general practitioner records, maternity passports, and maternal interviews before or after birth.[17] Norway medication exposures were based on first trimester prescription redemption records. Emilia Romagna did not have medication information for TOPFA. All first trimester medication exposures were recorded using the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. This is a hierarchical system which categorizes substances according to the organ or system on which they act (1st level) and their therapeutic (2nd level), pharmacological (3rd level) and chemical properties (4th and 5th level). First trimester was defined as the period from the first day of the last menstrual period to the end of gestational week 12. Medications taken in the second or third trimester or where the timing was unknown were excluded.

Maternal illnesses before pregnancy, which may affect fetal development, and illnesses occurring during the first 20 weeks of pregnancy were recorded, mostly prospectively from maternity records, using ICD-9/ICD-10 codes.[16] Registries not recording maternal illness were excluded from this analysis. In Norway, data were limited to maternal pregestational diabetes, asthma, epilepsy and pre-eclampsia so data from this registry were excluded from all other maternal illness analyses. See Supporting Figure 1 for the number of fetuses involved at each stage.

Literature review to identify signals

A literature review was conducted to identify all first trimester medication exposures or maternal illnesses that were previously reported to be associated with gastroschisis. Medline, Embase and PubMed were searched, with no date or language limits. The search, detailed in Supporting Appendix 1 and Supporting Figures 2 and 3, was last updated on the 13/11/2015. Supporting Tables 1 and 2 report the positive associations, or signals, identified by individual studies.

Seventeen case-control studies and one cohort study reported associations between gastroschisis and 20 medications/medication groups. Seven case-control and 2 cohort studies reported associations between gastroschisis and 19 maternal illnesses/groups of illnesses. A number of reported associations were not explored due to insufficient exposures in the dataset.

Statistical analysis

All analyses were conducted in Stata/SE 12.1 (StataCorp LP, USA). Prevalence rates, per 10,000 births were calculated as the (number of cases (Live Births + Still Births + TOPFA)/the number of births (Live Births + Still Births)) x 10,000.

Odds Ratios (ORs) were calculated for each of the medication exposure and maternal illness signals described in the literature where there were at least 3 observed, or 3 expected, gastroschisis cases in the EUROmediCAT database. If the signal was at the higher level, component groups were considered 'signal components' and are indicated as such in the tables e.g. depression was considered a component of the 'any mental disorder' signal. In addition, all medication exposures at the 5th and 4th ATC level and maternal illness, before or during pregnancy, with at least 3 observed, or 3 expected, gastroschisis cases were included in an exploratory signal generating analysis. If the same number of gastroschisis cases were exposed at the 4th and 5th level, the 4th level exposure was not investigated.

Logistic regression was used to calculate crude and adjusted ORs, and 95% CIs, for each exposure. Adjustment was made for maternal age group (<20, 20-24, 25-29 and 30+), registry and time period (1995-2000, 2001-2006 and 2007-2012). Likelihood ratio tests were used to assess interactions between maternal age and exposure variables.

For the medication exposures, sensitivity analyses were conducted 1) excluding those with pregestational or gestational diabetes, antidiabetic or anti-epileptic medication 2) excluding those whose medication exposure status was 'unknown' 3) excluding those not exposed to any medication (vitamin/mineral were not considered medications).

If a medication or maternal illness was known to be associated with a congenital anomaly subgroup included among the controls, a sensitivity analysis was conducted excluding the relevant congenital anomaly subgroup from the controls.

In recognition of the potential for multiple testing to generate significant results by chance, the need to avoid overreliance on significance testing[23,24] and the low power of analyses of rare exposures, we pre-specified criteria for interpretation of the results. We considered a signal from the literature to be 'supported' if the aOR ≥1.5 and the CI excluded 1. If the aOR was ≥1.5 and the CIs did not exclude 1 the signal was 'weakly supported'. New signals generated in the exploratory analysis were only considered if the aOR was ≥1.5 with CI excluding 1. Where the lower 95% CI of a new signal was not ≥1.5, generated signals were considered weak. We did not consider aORs <1.5 for signal evaluation or generation due to the small number of gastroschisis cases and the greater potential for confounding.

All medication and maternal illness exposures found to be associated with gastroschisis were validated by confirming the gastroschisis diagnosis, medication/illness exposure and timing of the exposure with the registries. The ratio of gastroschisis cases isolated/potentially multiply malformed was explored for associations with 10 or more exposures to identify any large disproportion.

Ethics

Ethical approval was provided by the University of Ulster Nursing Research Governance Filter Committee.

Results

Gastroschisis population

Excluding those with chromosomal/monogenic syndromes there were 1,587 gastroschisis cases across the 18 EUROmediCAT registries (1995-2012), for a total prevalence of 2.0 [95% CI 1.9, 2.1] gastroschisis cases per 10,000 births. The prevalence of gastroschisis varied across the registries (Table 1).

After exclusions, 1,577 gastroschisis cases, 83.0% of which were isolated, were compared to 153,357 non-chromosomal/monogenic controls. Of the gastroschisis cases 85% were live births, 4% stillbirths and 11% TOPFAs. 69% of cases were prenatally diagnosed (including TOPFA). Excluding TOPFAs 60% of cases were preterm (<37 gestational weeks) and 63% low birthweight (<2500g). Adjusting for registry and time period, cases were more likely to have been born to young mothers [<20, aOR 5.76, 95% CI 4.93, 6.72; 20-24, aOR 2.76, 95% CI 2.42-3.15] and less likely to have been born to older mothers [30+, aOR 0.44, 95% CI 0.38-0.53], compared to mothers aged 25-29.

Medication exposures: Signal evaluation

The signal for antidepressants was supported (Table 2). The majority of antidepressant exposures were to selective serotonin reuptake inhibitors (SSRIs) with fluoxetine, citalopram and sertraline all associated with gastroschisis (Table 2). After excluding congenital heart disease controls due to their putative association with SSRIs,[12,25] the OR was essentially unchanged (aOR 2.40, 95% CI 1.36, 4.27). Antidepressant, and SSRI exposure, were twice as

prevalent among mothers 30+ years old than among those <20, but there was no evidence of an interaction between maternal age and antidepressant exposure in their effect on gastroschisis risk (Likelihood-ratio test $\chi 2$ (3df) 2.77, P=0.43) or between maternal age and SSRI exposure (Likelihood-ratio test $\chi 2$ (3df) 1.58, P=0.66).

The signal for oral contraceptives was supported (Table 2) with 8 of the 10 gastroschisis cases exposed to the combined oral contraceptive levonorgestrel and ethinylestradiol. Exposure to an oral contraceptive was twice as prevalent among mothers <20 than among those 30+, but there was no evidence of an interaction between maternal age and oral contraceptive exposure (Likelihood-ratio test $\chi 2$ (2df) 0.85, P=0.66).

The signal for topical antivirals was supported (Table 2) but there were insufficient exposures to test the antiherpetic medication signal.

Signals relating to the analgesics paracetamol, nonsteroidal anti-inflammatory drugs, diclofenac, ibuprofen, opioid analgesics and codeine combinations excluding psycholeptics were weakly supported (Table 2). There was no support for the aspirin or salicylate signals.[26,27]

There was no support for the signals for asthma medications, either all asthma medications, inhaled $\beta 2$ agonists[28], bronchodilators,[29] or salbutamol and gastroschisis (Table 2). Excluding from controls anomalies previously associated with asthma medication[28] produced the same results.

Table 2. The association between Gastroschisis and medications with signals in the literature: number of exposures, number of Gastroschisis cases exposed, crude and maternal age, registry and time adjusted Odds Ratios for main and sensitivity analyses

	Exposed in dataset	Gastro-schisis cases exposed	Main Analysis		Sensitivity analyses							
			Complete dataset		Excluding unknown medication exposures		Only medication exposed		Excluding diabetes and Anti-Epileptic medication exposed			
			Crude OR [95% CI]	Adjusted OR [95% CI]	Crude OR [95% CI]	Adjusted OR [95% CI]	Crude OR [95% CI]	Adjusted OR [95% CI]	Exposed in dataset	Gastro-schisis exposed	Crude OR [95% CI]	Adjusted OR [95% CI]
Aspirin	577	2	0.34 [0.08, 1.36]	0.59 [0.15, 2.37]	0.30 [0.08, 1.22]	0.52 [0.13, 2.11]	0.31 [0.08, 1.25]	0.51 [0.12, 2.08]	536	2	0.36 [0.09, 1.45]	0.62 [0.15, 2.48]
Aspirin or Ibuprofen	825	6	0.72 [0.32, 1.60]	1.00 [0.44, 2.25]	0.64 [0.29, 1.44]	0.91 [0.40, 2.05]	0.66 [0.29, 1.48]	0.86 [0.37, 1.95]	775	6	0.75 [0.34, 1.68]	1.03 [0.46, 2.31]
Ibuprofen	249	4	1.60 [0.60, 4.30]	1.54 [0.56, 4.20]	1.44 [0.53, 3.87]	1.44 [0.53, 3.96]	1.49 [0.55, 4.05]	1.30 [0.47, 3.60]	240	4	1.64 [0.61, 4.40]	1.55 [0.57, 4.24]
NSAIDs	595	10	1.68 [0.90, 3.14]	1.81 [0.95, 3.43]	1.51 [0.80, 2.83]	1.71 [0.89, 3.27]	1.58 [0.83, 3.00]	1.56 [0.81, 3.02]	573	10	1.72 [0.92, 3.22]	1.84 [0.97, 3.49]
Diclofenac[a]	150	4	2.69 [0.99, 7.27]	2.70 [0.98, 7.45]	2.41 [0.89, 6.53]	2.77 [1.00, 7.72]	2.52 [0.92, 6.86]	2.46 [0.87, 6.92]	143	4	2.78 [1.03, 7.53]	2.74 [0.99, 7.57]
Salicylates	626	3	0.47 [0.15, 1.46]	0.77 [0.25, 2.42]	0.42 [0.14, 1.31]	0.69 [0.22, 2.17]	0.43 [0.14, 1.35]	0.60 [0.19, 1.92]	585	3	0.50 [0.16, 1.55]	0.80 [0.26, 2.51]
Paracetamol	1,064	15	1.40 [0.84, 2.34]	1.66 [0.99, 2.81]	1.26 [0.75, 2.11]	1.43 [0.84, 2.42]	1.32 [0.78, 2.24]	1.27 [0.73, 2.19]	1,038	15	1.42 [0.85, 2.37]	1.69 [1.00, 2.85]

Opioid analgesics	292	7	2.76 [1.36, 5.58]	1.98 [0.97, 4.07]	2.48 [1.22, 5.03]	1.77 [0.86, 3.68]	2.61 [1.28, 5.35]	1.56 [0.74, 3.28]	280	8	2.85 [1.41, 5.76]	2.05 [1.00, 4.22]
Codeine, combinations excluding psycholeptics[a]	181	5	2.79 [1.14, 6.79]	1.84 [0.74, 4.57]	2.51 [1.03, 6.11]	1.68 [0.67, 4.21]	2.62 [1.07, 6.44]	1.47 [0.58, 3.72]	174	5	2.86 [1.17, 6.97]	1.93 [0.78, 4.78]
Anti-depressants	777	16	2.07 [1.26, 3.41]	2.03 [1.22, 3.38]	1.86 [1.13, 3.07]	1.73 [1.04, 2.90]	1.99 [1.19, 3.32]	1.64 [0.96, 2.81]	709	16	2.24 [1.36, 3.69]	2.14 [1.28, 3.56]
SSRIs[a]	506	13	2.60 [1.49, 4.51]	2.45 [1.39, 4.33]	2.34 [1.34, 4.07]	2.12 [1.20, 3.75]	2.49 [1.41, 4.39]	2.03 [1.12, 3.68]	471	13	2.75 [1.58, 4.79]	2.55 [1.44, 4.49]
Fluoxetine[a]	113	4	3.60 [1.33, 9.78]	3.03 [1.09, 8.45]	3.24 [1.19, 8.80]	2.53 [0.90, 7.08]	3.38 [1.23, 9.25]	2.20 [0.77, 6.25]	104	4	3.87 [1.42, 10.52]	3.15 [1.13, 8.79]
Citalopram[a]	144	5	3.53 [1.44, 8.63]	3.06 [1.23, 7.61]	3.17 [1.30, 7.77]	2.44 [0.97, 6.10]	3.32 [1.35, 8.20]	2.29 [0.89, 5.88]	136	5	3.69 [1.51, 9.03]	3.11 [1.25, 7.74]
Sertraline[a]	74	3	4.14 [1.30, 13.17]	4.19 [1.27, 13.76]	3.72 [1.17, 11.84]	3.74 [1.14, 12.31]	3.88 [1.21, 12.42]	3.86 [1.15, 12.94]	68	3	4.46 [1.40, 14.21]	4.35 [1.32, 14.33]
Topical antivirals[a]	82	3	3.72 [1.17, 11.81]	5.31 [1.63, 17.33]	3.35 [1.05, 10.62]	5.47 [1.65, 18.15]	3.49 [1.09, 11.13]	5.13 [1.53, 17.22]	79	3	3.81 [1.20, 12.10]	5.40 [1.65, 17.64]
All Asthma Medications	1,455	23	1.58 [1.04, 2.40]	1.30 [0.85, 1.99]	1.42 [0.94, 2.16]	1.10 [0.71, 1.69]	1.52 [0.98, 2.35]	0.93 [0.58, 1.48]	1,385	23	1.64 [1.08, 2.48]	1.35 [0.88, 2.06]
Inhaled β2 agonists	888	16	1.81 [1.10, 2.97]	1.29 [0.77, 2.14]	1.62 [0.99, 2.68]	1.08 [0.65, 1.80]	1.72 [1.03, 2.88]	0.90 [0.52, 1.55]	844	16	1.87 [1.14, 3.08]	1.33 [0.80, 2.21]

Bronchodilators[b]	820	16	1.96 [1.19, 3.22]	1.44 [0.87, 2.40]	1.76 [1.07, 2.91]	1.21 [0.72, 2.02]	1.88 [1.12, 3.14]	1.01 [0.58, 1.75]	776	16	2.04 [1.24, 3.36]	1.50 [0.90, 2.49]
Salbutamol[a]	782	14	1.79 [1.05, 3.05]	1.29 [0.75, 2.21]	1.61 [0.95, 2.75]	1.07 [0.62, 1.84]	1.70 [0.99, 2.94]	0.88 [0.49, 1.57]	740	14	1.87 [1.10, 3.18]	1.33 [0.78, 2.30]
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics[a]	214	3	1.39 [0.45, 4.36]	1.35 [0.43, 4.30]	1.25 [0.40, 3.92]	1.23 [0.39, 3.95]	1.30 [0.41, 4.08]	1.11 [0.34, 3.61]	207	3	1.42 [0.45, 4.44]	1.36 [0.43, 4.34]
Glucocorticoids[a]	530	4	0.74 [0.28, 1.99]	0.69 [0.26, 1.87]	0.67 [0.25, 1.79]	0.57 [0.21, 1.55]	0.68 [0.25, 1.85]	0.49 [0.18, 1.34]	505	4		
Beclometasone[a]	296	1	0.33 [0.05, 2.36]	0.30 [0.04, 2.17]	0.30 [0.04, 2.12]	0.24 [0.03, 1.73]	0.30 [0.04, 2.18]	0.20 [0.03, 1.46]	283	1	0.34 [0.05, 2.44]	0.32 [0.04, 2.27]
Oral Contraceptives	363	10	2.79 [1.48, 5.23]	2.17 [1.13, 4.18]	2.51 [1.33, 4.72]	2.24 [1.15, 4.37]	2.65 [1.39, 5.05]	2.08 [1.05, 4.12]	348	10	2.87 [1.53, 5.39]	2.25 [1.17, 4.33]
Progestogens and estrogens, fixed combinations[a]	270	8	3.00 [1.48, 6.08]	2.22 [1.07, 4.60]	2.70 [1.33, 5.47]	2.20 [1.05, 4.62]	2.85 [1.39, 5.83]	2.02 [0.95, 4.29]	261	8	3.06 [1.51, 6.20]	2.29 [1.10, 4.74]
Levonorgestrel and Ethinylestradiol[a]	163	8	5.08 [2.49, 10.35]	4.02 [1.90, 8.50]	4.57 [2.24, 9.33]	4.07 [1.90, 8.72]	4.84 [2.34, 9.98]	3.71 [1.70, 8.12]	161	8	5.07 [2.48, 10.33]	4.06 [1.92, 8.60]

It was not possible to test a number of signal medications due to insufficient numbers of exposed gastroschisis cases [n]: dihydrocodeine [n=0], paroxetine [n=0], venlafaxine [n=1], antiherpetics [n=2], diphenhydramine [n=0], phenylpropanolamine [n=0], pseudoephedrine [n=0], oral decongestants [n=0].

[a] Medication or medication group which is a component of a medication signal and had more than 3, or 3 expected, exposures at the 4th or 5th ATC level

[b] Salbutamol, salmeterol, pirbuterol, ipratropium bromide, ephedrine, epinephrine, theophylline

Maternal Illness: Signal Evaluation

Cases were less likely than controls to have had maternal exposure to 'any (pregestational or gestational) diabetes' and pregestational diabetes (Table 3 and Supporting Table 4). Excluding from controls anomalies previously associated with diabetes[30] somewhat decreased the size of the negative association [aOR 0.41, 95% CI 0.17, 0.99 and aOR 0.20, 95% CI 0.03, 1.45 respectively].

There was weak support for an association with 'any mental disorder', depression and 'mental and behavioral disorders associated with the puerperium' (Table 3). Half of the gastroschisis cases with depression and a third of those with 'mental and behavioral disorders associated with the puerperium' were exposed to an antidepressant in the first trimester. The prevalence of these mental disorders varied little across maternal age groups.

Signals for sexually transmitted infections (STIs) excluding and including yeast/vaginal infections were supported but there was no evidence for an association with urinary tract infection.[13,31] STIs including yeast/vaginal infections were six times as prevalent among mothers <20 than among mothers 30+ but there was no evidence of an interaction (Likelihood-ratio test $\chi 2$ (2df) 2.97, P=0.23). The STI diagnosis includes genital herpes but there were not enough exposures to genital herpes to explore this exposure directly.

Table 3. The association between Gastroschisis and maternal illness: ICD 9 and ICD 10 code/s, number of exposures in the dataset, number of Gastroschisis cases exposed, crude and adjusted ORs

Maternal illness signal	ICD-9	ICD-10	Exposures in dataset	Gastroschisis cases exposed	Crude OR [95% Confidence Interval]	Adjusted[a] OR [95% Confidence Interval]
Any (pregestational or gestational) diabetes	250, 648.0, 648.8	E10-14, O24	2378	5	0.22 [0.09, 0.52]	0.31 [0.13, 0.75]
Pregestational diabetes[bc]	250	E10-14	882	1	0.11 [0.02, 0.82]	0.13 [0.02, 0.92]
Gestational diabetes [c]	648.8	O244	1150	4	0.36 [0.14, 0.97]	0.65 [0.24, 1.76]
Any mental disorder (psychoses, neurotic disorders, personality disorders, other nonpsychotic mental disorders, and mental retardation)	290-9, 300-3, 305-9,310-9	F00-F99	1113	20	1.94 [1.24, 3.04]	1.55 [0.98, 2.44]

Depression[c]	300.4, 311	F32-3	559	13	2.52 [1.45, 4.39]	2.52 [1.45, 4.39]
Mental and behavioral disorders associated with the puerperium, not elsewhere classified (postnatal/postpartum depression and puerperal psychosis)[c]	[d]	F53	41	3	8.32 [2.56, 27.01]	8.32 [2.56, 27.01]
Urinary tract infection (UTI)	646.6	O23	1211	13	1.14 [0.66, 1.98]	0.95 [0.54, 1.66]
Sexually transmitted infections (STIs)	090-097, 054.1, 131, 647.0-2	A50-A64, O98.1-3, M02.3	86	5	6.52 [2.64, 16.13]	2.85 [1.13, 7.24]
STIs including yeast/vaginal infections (vaginal candida)	090-097, 054.1, 131, 647.0-2, 112.1	A50-A64, O98.1-3, M02.3, B37.3	150	6	4.40 [1.94, 9.99]	2.52 [1.09, 5.85]

UTI or STIs	646.6, 090-097, 054.1, 131, 647.0-2	O23, A50-A64, O98.1-3, M02.3	1298	18	1.49 [0.93, 2.38]	1.17 [0.73, 1.89]
UTI or STIs including yeast/vaginal infections	646.6, 090-097, 054.1, 131, 647.0-2, 112.1	O23, A50-A64, O98.1-3, M02.3, B37.3	1355	18	1.42 [0.89, 2.28]	1.13 [0.70, 1.83]

[a] Adjusted for maternal age, registry and time period.

[b] Analysis includes data from Norway registry.

[c] Illness which is a component of an illness signal.

[d] ICD-9 and ICD-10 codes not comparable for this diagnosis so analysis was restricted to the ICD-9/10 code which produced the original signal.

Medication and maternal illness: Exploratory analyses

Thirty-nine non-signal ATC codes were tested for an association with gastroschisis in the exploratory analysis (Supporting Table 3). There were signals for vitamin E [aOR 5.74, 95% CI 1.68, 19.59, n=3] and bromhexine [aOR 29.48, 95% CI 8.24, 105.50, n=3], and weak signals for hydrocortisone [aOR 3.94, 95% CI 1.19, 13.01, n=3] and drotaverine [aOR 2.31, 95% CI 1.08, 4.97, n=7]. Caution should be used when interpreting the drotaverine and vitamin E signals. The drotaverine signal was not robust in the sensitivity analysis and two of the three cases involved in the vitamin E signal were also exposed to drotaverine.

Fourteen non-signal maternal illnesses were tested for an association with gastroschisis in the exploratory analysis (Supporting Table 4). Further maternal infections were associated with gastroschisis, producing a signal for acute tonsillitis [aOR 8.40, 95% CI 2.41, 29.31, n=3] and weak signals for ‘acute upper respiratory infections of multiple or unspecified sites’ [aOR 2.65, 95% CI 1.46, 4.81, n=13] and ‘bacterial infection of unspecified site’ [aOR 3.56, 95% CI 1.06, 11.98, n=3]. There were also weak signals for hemorrhage in early pregnancy [aOR 1.52, 95% CI 1.01, 2.31, n=27] and ‘gastritis and duodenitis’ [aOR 3.12, 95% CI 1.11, 8.75, n=4].

There was no disproportion in the ratio of isolated to potentially multiply malformed gastroschisis cases for any of the medication or maternal illness signals with more than 10 exposed cases.

Comments

Gastroschisis is a rare anomaly, occurring on average in one in every 5,000 births in Europe. We have added to a growing evidence base that the maternofetal environment is important in the causation of gastroschisis, specifically in respect to maternal illness and medication, pointing to the need for greater understanding of causal pathways. Among teenage mothers, one in every 870 births was affected by gastroschisis, either due to their greater vulnerability to, or more frequent exposure to these and other unmeasured factors acting singly or in combination.

Mental illness is common among women of reproductive age with an estimated 7-11% of pregnant women affected by depression in their first trimester.[32] Antidepressants are also increasingly being used during pregnancy, with SSRIs the most frequently prescribed.[33,34] Our study confirmed that first trimester exposure to antidepressants, specifically SSRIs,[12,25] and mental disorders,[31] including depression, were associated with gastroschisis. As antidepressant use is more prevalent among older mothers this relationship is contrary to the known association between gastroschisis and young maternal age. A recent multi-country population based cohort study found a low and non-significant OR for SSRIs, particularly with sibling controls,[35] but was much smaller and did not include stillbirths and TOPFAs. We could not effectively control for confounding by indication due to incomplete ascertainment of both medication and illness exposures. We had no information on lifestyle factors, such as smoking,[9] alcohol consumption[10] or illicit drug use[11] which could confound the association with mental health. Whatever the causal pathway, mothers with depression should be considered a high-risk group for gastroschisis.

First trimester exposure to oral contraceptives, mainly levonorgestrel and ethinylestradiol, was confirmed to be associated with gastroschisis.[36] Estrogen related

thrombosis has been proposed as one of the pathogenic mechanisms behind gastroschisis.[37] High estrogen levels are typical for young women in the early gestational stages when anomalies develop[6] and this hormonal mechanism may contribute to the high risk for young women. Alternatively, oral contraceptive exposure may be acting as a marker for an unplanned pregnancy with a suboptimal periconceptional environment.

Infections repeatedly showed associations with gastroschisis in our data, adding to the existing literature.[13,31,38] Maternal STI was associated with a 2½-3 times increased risk of gastroschisis. Further supporting evidence is provided by studies which found biological markers of recent chlamydia infection[39] and reactivation of previous herpes simplex virus type 2 infection[40] to be associated with gastroschisis. STIs may be one of the factors explaining the high risk of gastroschisis in young mothers. Both a direct effect and indirect effect of STI exposure, through immune and inflammatory responses, have been suggested.[13,39] While the association found for topical antivirals may be confounded by indication there is also the potential for medications used in the treatment of STIs to be contributing to the increased risk of gastroschisis. Interestingly, we found no supporting evidence for an association with urinary tract infections, contrary to some other studies.[13,31] There was new evidence in our data relating to acute tonsillitis and to a lesser degree respiratory infections, bacterial infections, and gastritis/duodenitis (which can be caused by helicobacter pylori infection). Maternal infection as indication may have confounded the signals we found for bromhexine, an expectorant, and drotaverine, an antispasmodic.

A number of analgesics were weakly associated with gastroschisis. We found weak evidence to support the signal for paracetamol and there is contradictory evidence relating to this association in the literature.[10,26,41] While we found a weak association with nonsteroidal

anti-inflammatory drugs generally, and ibuprofen and diclofenac specifically, both our study and another recent study[42] found no evidence to support the signals previously published for aspirin or salicylates.[26,43] There is known under ascertainment for over the counter medications in the EUROmediCAT database[17] and this will have reduced our power to detect an increased risk associated with these analgesics. If these analgesics were used during maternal infections, there is again the potential for confounding by indication.

Pregestational diabetes is a strong risk factor for a range of anomalies.[30] The signal for an increased risk of gastroschisis in those with (pregestational or gestational) diabetes arose in a study with unreliable diabetes ascertainment.[44] We found no evidence for an increased risk of gastroschisis among those with either any (pregestational or gestational) diabetes or pregestational diabetes. Instead, in agreement with another study which was able to control for maternal body mass index,[31] we found evidence for a protective effect of diabetes. While the magnitude of the effect decreased, it persisted after correcting for the fact that our malformed controls contained anomalies associated with pregestational diabetes. Further evidence to support this apparent protective effect should be sought but it does fit with the known negative association between gastroschisis and high maternal body mass index.[45]

No association was found between asthma medications, either all asthma medications, inhaled β2 agonists or bronchodilators, and gastroschisis. This signal arose in a study of bronchodilators,[29] but previous evidence from EUROmediCAT data has been inconsistent.[28,46]

In a previous study,[5] we established that the geographical variation within Europe persisted independently of maternal age differences between populations. We have shown here that

many of the exposures conferring risk are more common among young mothers. Our ability to shed light on the extent to which maternal illness or medication contribute to maternal age and geographic variation in prevalence is limited due to incomplete ascertainment of both these exposures in cases and controls, and variation in ascertainment between registries.

Strengths and weaknesses

EUROmediCAT's international population based database covers a very large population suitable for studying a rare condition such as gastroschisis, contains detailed coding of all congenital anomalies[16] and includes TOPFA which constituted more than 11% of gastroschisis cases and 5% of controls. The data are standardized across the registries, although registers differ in their exposure ascertainment methodology.[16] Gastroschisis cases identified prenatally were confirmed after live/stillbirth. Practice following TOPFA varies but usually either an external or full post-mortem take place. Less than 1% of gastroschisis cases occurred in very early TOPFA (before 13 gestational weeks) where diagnostic accuracy may be less certain. Although the distinction between gastroschisis and omphalocele was a concern in early studies[4] the data analysed here started in 1995 when diagnostic accuracy was good. Use of the BPA extension to ICD-9 ensured that gastroschisis and omphalocele were recorded separately and we excluded all of those with poorly specified abdominal wall diagnoses from both cases and controls.

There is no information on confounders such as smoking or alcohol, and limited ability to control for confounding by indication. It was therefore not possible to disentangle the relative contributions of maternal ill health and the medications used in its treatment. As maternal illness during pregnancy is recorded up to the 20th gestational week acute illnesses,

such as infections, may have occurred outside the first trimester, in both cases and controls. This will be less of a concern for chronic illnesses such as depression.

Teratogen non-specificity bias, where the exposure in question is associated with both cases and controls, may have diluted ORs[20]. However, when the control group was restricted to address this issue the ORs changed very little suggesting that the wide variety of anomalies within our control group negated this problem.

There is known under ascertainment of medication exposure in the EUROmediCAT database, particularly for over the counter medications.[17,47] This will have reduced the power of our analysis but should not have introduced bias as cases and controls had equal probability of having their exposure recorded.[20]

Due to multiple testing of many exposures, some chance positive associations are likely, but we found more positive associations than expected by chance. We mitigated this by clearly specifying our prior hypotheses, to be tested as signals from the literature, examining patterns of exposures (e.g. mental health or infection related) and pre-specifying criteria for interpretation of the strength of the evidence.

Conclusion

Our study adds strong evidence that antidepressants and/or mental health disorders, a variety of maternal infections, particularly STIs, and continuation of oral contraceptives in early pregnancy are associated with gastroschisis. Better understanding of these risk factors, in particular the complex of risk factors more prevalent among young mothers, who are at

higher risk of gastroschisis, should help target supportive services reducing the prevalence of gastroschisis and improving maternal and fetal health more generally.

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Supporting Information

Supporting Appendix 1. Literature Review to Identify 'Signals' to be Tested.

Medline, Embase and PubMed were searched, with no date or language limits. For medication exposures the search term 'gastroschisis' was combined with 'drug', 'medication', 'drug exposure', 'drug use' or 'prenatal drug exposure'. For maternal illnesses 'gastroschisis' was combined with 'disease', 'acute disease', 'chronic disease', 'maternal disease', 'diseases', 'maternal illness', 'acute illness' or 'chronic illness'. The search was last updated on the 13/11/2015. Only full text articles of original studies exploring the risk of gastroschisis in humans were included. Where "drug" referred to illicit drugs, the information has not been used in this paper.

Supporting Table 1. Medications associated with gastroschisis in the literature, crude, and adjusted ORs and study details

Medication group	Medication/s	Exposed cases	Crude OR [95% Confidence Intervals]	Adjusted OR [95% Confidence Intervals]	Article	Country	Study	Years	Design	Maternal age adjustment
Analgesics	Aspirin	13		2.7[a] [1.2, 5.9]	Werler et al. 2002 [1]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1995-1999	Matched case-control (malformed and non-malformed)	Matched on maternal age
		7		20.4[b] [2.2, 191.5]	Draper et al. 2008 [2]	UK	Trent, Northern, and West Midlands Regional Congenital Anomaly Registers	2001-2003	Matched case-control	Matched on maternal age
		7	4.7 [1.2, 18.1]		Torfs et al. 1996 [3]	USA	California Birth Defects Monitoring Program	1989-1990	Matched case-control	Matched on maternal age
	Aspirin or ibuprofen	13	5.2 [1.9, 14.6]	4.6[c] [1.4, 14.7]						
	Ibuprofen	6	4.0 [1.0, 16.0]							
				1.6[d] [1.2, 2.1]	Mac Bird et al. 2009 [4]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes

	NSAIDs	151		1.4[e] [1.1, 1.7]	Werler et al. 2009 [5]	USA	National Birth Defects Prevention Study	1997-2003	Matched case-control	Matched on maternal age
	Salicylates	5	3.3 [1.1, 9.8]	3.5[f] No CI provided	Martínez-Frías et al. 1997 [6]	Spain	Spanish Collaborative Study of Congenital Malformations	1976-1996	Case-Control	Yes
	Paracetamol	120		1.5)[a] [1.1, 2.2]	Werler et al. 2002 [1]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1995-1999	Matched case-control (malformed and non-malformed)	Matched on maternal age
	Opioid analgesics	26		1.8[g] [1.1, 2.9]	Broussard et al. 2011 [7]	USA	National Birth Defects Prevention Study	1997-2005	Case-control	Yes
	Dihydrocodeine	15	3.3 [1.8, 6.1]							
Anti-depressants	Antidepressants	22	4.7 [2.6, 8.3]	4.0[h] [1.4, 11.8]	Skarsgard et al. 2015 [8]	Canada	Canadian Pediatric Surgery Network/ Canadian Community Health Survey	2006-2012	Cohort	Yes
	The Paroxetine	5		2.9[i] [1.0, 8.4]	Alwan et al. 2007 [9]	USA	National Birth Defects Prevention Study	1997-2002	Case-Control	No

		13		2.5[j] [1.2, 4.8]	Reefhuis et al. 2015 [10]	USA	National Birth Defects Prevention Study	1997-2009	Case-control	No
	Venlafaxine	6	3.8 [1.2, 10.5]	5.7[k] [1.8, 15.9]	Polen et al. 2013 [11]	USA	National Birth Defects Prevention Study	1997-2007	Case-control	Yes
Anti-herpetics	Antiherpetics (aciclovir, valaciclovir or famciclovir)	4	3.6 [1.1, 11.5]	4.7[l] [1.2, 19.0]	Ahrens et al. 2013 [12]	USA	National Birth Defects Prevention Study	1997-2007	Case-control	Yes
Anti-histamines	Diphenhydramine	16		2.0[m] [1.0, 3.9]	Gilboa et al. 2009 [13]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes
Asthma medication	Any asthma medication[uv]	22		1.6[o] [1.0, 2.5]	Garne et al. 2015 [14]	Europe	EUROmediCAT	1995-2010	Case-malformed control	Yes
	Inhaled β2 agonists[v]	19		1.9[p] [1.1, 3.2]						
	Bronchodilators (Salbutamol, salmeterol, pirbuterol, ipratropium bromide, ephedrine, epinephrine, theophyline)	17	1.9 [1.1, 3.3]	2.1[q] [1.2, 3.6]	Lin et al. 2008 [15]	USA	National Birth Defects Prevention Study	1997-2002	Case-control	Yes

Contracep-tives	Oral contraceptives	40		1.8[r] [1.3, 2.7]	Waller et al. 2010 [16]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes
Deconges-tants	Phenylpropan-olamine	5	10.0 [1.2, 85.6]		Torfs et al. 1996 [3]	USA	California Birth Defects Monitoring Program	1989-1990	Matched case-control	Matched on maternal age
	Pseudoephedrine	9		Relative risk 3.2[s] [1.3, 7.7]	Werler et al. 1992 [17]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1976-1990	Case-malformed control	Yes
		35		1.8[a] [1.0, 3.2]	Werler et al. 2002 [1]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1995-1999	Matched case-control (malformed and non-malformed)	Matched on maternal age
	Oral decongestants (pseudoephedrine, phenylephrine and phenylpropan-olamine)	20		1.7[t] [1.0, 2.9]	Yau et al. 2013 [18]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1993-2010	Case-control	Yes

a Adjusted for education, income, medication use, illness, illicit drug use, and cigarette smoking. Control group consisted of both malformed and non-malformed infants
b Adjusted for use of any recreational drug, use of a vasoactive recreational drug, BMI, marital status, homeowner status, history of gynaecologic infection/disease and cigarette smoking.
c Adjusted for smoking status, prenatal care, mothers father absent during youth, family income and exposure to solvents, decongestants, x-rays and 'cocaine and other drugs'.
d Adjusted for race/ethnicity, plurality, family income, parity, maternal age, fever, infant sex, any maternal drinking, maternal smoking, maternal BMI, gestational diabetes, pre-existing diabetes, folic acid supplementation, study centre and exposure to pseudoephedrine, aspirin, paracetamol, naproxen, marijuana, and cocaine
e Adjusted for maternal age at delivery and state of residence by stratification and for race/ethnicity, BMI, education, alcohol use, oral contraceptive use, folic acid supplementation
f Adjusted for maternal age and smoking status
g Adjusted for maternal age, race/ethnicity, education, presence or absence of pre-pregnancy obesity, presence or absence of periconceptional smoking, and study centre
h Adjusted for area, maternal age, alcohol, tobacco, illicit drug use, pregestational/gestational diabetes and folic acid
i Adjusted for maternal race or ethnic group, maternal obesity, maternal smoking and family income. Infants whose mothers had pregestational diabetes mellitus type 1 or 2 were excluded
j Adjusted for maternal race/ethnicity, maternal education, obesity, and smoking
k Adjusted for maternal age and race/ethnicity
l Adjusted for maternal age at delivery and BMI before conception
m Adjusted for maternal age, maternal race or ethnicity, maternal education, entry into prenatal care, parity, household income, and study centre, periconceptional folic acid use, smoking, and alcohol intake
n Includes all medications starting with the ATC code R03. Note this dataset overlaps to some extent with that used in this study
o Adjusted for registry and maternal age
p Adjusted for registry, maternal age and use of corticosteroids
q Adjusted for maternal age, ethnicity, educational level, smoking, folic acid, and any of the following vasoactive medications: aspirin, ibuprofen, acetaminophen, amoxicillin, pseudoephedrine, phenylpropanolamine, and methylenedioxymethamphetamine
r Adjusted for maternal age
s Adjusted for maternal age, years of education, parity, alcohol consumption, influenza in the first trimester, interview year, study centre and exposure to salicylates, paracetamol, ibuprofen, phenylpropanolamine, other oral decongestants, other nasal/ophthalmic decongestants, antihistamines, antibiotics and oral contraceptives
t Adjusted for maternal age, pre-pregnancy weight, educational level, and smoking
u Includes all medications starting with the ATC code R03
v Note this dataset overlaps to some extent with that used in this study

Supporting Table 2. Maternal illnesses associated with gastroschisis in the literature, crude, and adjusted ORs and study details

Maternal illness	Maternal disease	Exposed cases	Crude OR [95% Confidence Intervals]	Adjusted OR [95% Confidence Intervals]	Article	Country	Study	Years	Design	Maternal age adjustment
Low BMI	Low BMI[a] (<18.1)	16	3.16 [1.38, 7.26]	3.20[b] [1.38, 7.42]	Lam et al. 1999 [19]	USA	California Birth Defects Monitoring Programme	1988-1990	Matched case-control	Matched on maternal age
Diabetes	Any (pregestational or gestational) diabetes	19	2.34 [1.39, 3.98]	2.81[c] [1.42, 5.57]	Skarsgard et al. 2015 [8]	Canada	Canadian Pediatric Surgery Network/ Canadian Community Health Survey	2006-2012	Cohort	Yes
Other endocrine disorders	'Other endocrine disorder' (pancreatic, parathyroid, pituitary, thymus, adrenal, ovarian, polyglandular, and other endocrine dysfunction.)	6	1.5 [0.7, 3.4]	3.2 for those 20-24[d] [1.2, 8.5]	Baer et al. 2015 [20]	USA	California Office of Statewide Health Planning and Development Livebirth Cohort	2005-2010	Cohort study	Stratified by age group
Mental disorder	Mental disorder (psychoses, neurotic disorders, personality disorders, other nonpsychotic mental disorders, and mental retardation)	75	1.8 [1.4, 2.3]	2.1 for those >24[e] [1.4, 3.2]	Baer et al. 2015 [20]	USA	California Office of Statewide Health Planning and Development Livebirth Cohort	2005-2010	Cohort study	Stratified by age group
Previous pregnancy loss	Previous pregnancy loss[a]			2.34[f] (malformed controls) [1.37, 3.97] 3.43 (non-malformed controls) [2.07, 5.66]	Rittler et al. 2015 [21]	South America	Estudio Colaborativo Latino Americano de Malformaciones Congenitas	1995-2010	Case-control[p]	Only those <20 included in study
Infection	Chest cold	5	16.8 [1.98, 150.3]		Elliott et al. 2009 [22]	USA	2 medical centres in Nevada	2007-2008	Matched case-control	Matched on maternal age

	Sore throat	5	12.7 [1.3, 122.5]							
	Viral infection 'complicating pregnancy'	40	1.8 [1.3, 2.5]	2.0 for those 20-24[g][1.3, 3.3] 2.1 for those >24[h] [1.3, 3.6]	Baer et al. 2015 [20]	USA	California Office of Statewide Health Planning and Development Livebirth Cohort	2005-2010	Cohort study	Stratified by age group
	Other specified infection complicating pregnancy (including tuberculosis, malaria, rubella, and other specified infectious and parasitic diseases)	17	1.9 [1.2, 3.1]	2.0 for those 20-24[i] [1.0, 3.8]	Baer et al. 2015 [20]	USA	California Office of Statewide Health Planning and Development Livebirth Cohort	2005-2010	Cohort study	Stratified by age group
	UTI	60	1.9 [1.5, 2.6]	1.4[j] [1.0, 2.0]	Feldkamp et al. 2008 [23]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes
	UTI	127	1.9 [1.6, 2.3]	1.5 for those <20[k] [1.1, 1.9]	Baer et al. 2015 [20]	USA	California Office of Statewide Health Planning and Development Livebirth Cohort	2005-2010	Cohort study	Stratified by age group
	UTI	33	3.6 [2.5, 5.4]	2.3[l] [1.5, 3.5]	Yazdy et al. 2014 [24]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1998-2010	Case-control	Yes
	Genital herpes (including those with use of Antiherpetic medication)	6	3.2 [1.3, 8.1]	4.7[m] [1.7, 13.3]	Ahrens et al. 2013 [12]	USA	National Birth Defects Prevention Study	1997-2007	Case-control	Yes
	Genital herpes (excluding those with use of Antiherpetic medication)	16	2.6 [1.5, 4.6]	3.0[m] [1.6, 5.7]						

	STI	17	2.7 [1.7, 4.4]	2.0 for those <20[n] [1.1, 3.6]	Baer et al. 2015 [20]	USA	California Office of Statewide Health Planning and Development Livebirth Cohort	2005-2010	Cohort study	Stratified by age group
	STI	14	1.7 [1.0, 3.0]	1.3[h] [0.7, 2.3]	Feldkamp et al. 2008 [23]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes
	STI including yeast/vaginal infections	33	1.3 [1.1, 1.6]	1.2[j] [1.0, 1.5]	Yazdy et al. 2014 [24]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1998-2010	Case-control	Yes
	UTI or STI	81	2.0 [1.6, 2.6]	1.5[h] [1.1, 1.9]	Feldkamp et al. 2008 [23]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes
	UTI or STI including yeast/vaginal infections	73	2.4 [1.8, 3.1]	1.8[j] [1.3, 2.4]	Yazdy et al. 2014 [24]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1998-2010	Case-control	Yes
	UTI & STI	7	6.8 [2.6, 17.5]	4.0[h] [1.4, 11.6]	Feldkamp et al. 2008 [23]	USA	National Birth Defects Prevention Study	1997-2003	Case-control	Yes
	UTI & STI including yeast/vaginal infections	7	1.5 [1.1, 1.9]	1.2[j] [0.9, 1.6]	Yazdy et al. 2014 [24]	USA and Canada	Slone Epidemiology Center Birth Defects Study	1998-2010	Case-control	Yes
	Prior history of gynaecologic infection or disease (recurrent UTI, chlamydia or abnormal smear prior to current pregnancy)[a]	18	2.8 [1.4, 5.5]	2.6[o] [1.2, 5.6]	Draper et al. 2008 [2]	UK	Trent, Northern, and West Midlands Regional Congenital Anomaly Registers	2001-2003	Matched case-control	Matched on maternal age

a Not considered a maternal illness within the EUROCAT illness variable and therefore not analysed.
b Adjusted for maternal age and ethnicity
c Adjusted for area, maternal age, alcohol, tobacco, illicit drug use, depression medication and folic acid
d Adjusted for race/ethnicity, type of health insurance, education, parity, mother's country of birth, obesity, any diabetes, any gestational hypertension, viral infection and other specified infection
e Adjusted for race/ethnicity, type of health insurance, education, parity, obesity, smoking, any gestational hypertension and viral infection
f Adjusted for hospital, year of birth, young paternal age, maternal education, paternal education, paternal occupation, consanguinity, race/ethnicity, short inter-birth interval, change in paternity, parity, duration of cohabitation, prenatal control, medication, maternal illness, smoking, alcohol and illicit drugs
g Adjusted for adjusted for race/ethnicity, type of health insurance, education, parity, mothers country of birth, obesity, any diabetes, any gestational hypertension, other specified infection and other endocrine disorder
h Adjusted for race/ethnicity, type of health insurance, education, parity, obesity, smoking, any gestational hypertension and mental disorder
i Adjusted for race/ethnicity, type of health insurance, education, parity, mother's country of birth, obesity, any diabetes, any gestational hypertension, viral infection and other endocrine disorder
j Adjusted for maternal age, BMI before conception, smoking, and Hispanic ethnicity
k Adjusted for adjusted for race/ethnicity, obesity, smoking, any gestational hypertension, sexually transmitted infection and drug dependency
l Adjusted for maternal age
m Adjusted for maternal age at delivery and BMI before conception
n Adjusted for race/ethnicity, obesity, smoking, any gestational hypertension, urinary tract infection and drug dependency
o Adjusted for use of any recreational drug, use of a vasoactive recreational drug, use of aspirin, BMI, marital status, homeowner status and cigarette smoking
p Malformed [omphalocele, spina bifida, hydrocephaly, cleft lip with or without cleft palate, and Down syndrome] and non-malformed controls

Supporting Table 3. Medication exploratory analysis results - crude and maternal age, registry and time adjusted ORs for main and sensitivity analyses

Medication/medication group	Main analysis				Sensitivity analyses							
	Complete dataset				Excluding unknown drug exposures		Only drug exposed		Excluding diabetes and AEDs			
	Exposed in dataset	Gastroschisis exposed	Crude OR [95% CI]	Adjusted OR [95% CI]	Crude OR [95% CI]	Adjusted OR [95% CI]	Crude OR [95% CI]	Adjusted OR [95% CI]	Exposed in dataset	Gastroschisis exposed	Crude OR [95% CI]	Adjusted OR [95% CI]
Hydrocortisone	108	3	2.8 [0.9, 8.8]	3.9 [1.2, 13]	2.5 [0.8, 7.9]	4.0 [1.2, 13.2]	2.6 [0.8, 8.4]	2.8 [0.9, 9.2]	104	3	2.9 [0.9, 9.1]	4.0 [1.2, 13.1]
Combinations and complexes of aluminium, calcium and magnesium compounds	339	1	0.3 [0.0, 2.1]	0.6 [0.1, 4.6]	0.3 [0.0, 1.9]	0.6 [0.1, 4.0]	0.3 [0.0, 1.9]	0.4 [0.1, 2.7]	329	1	0.3 [0.0, 2.1]	0.6 [0.1, 4.6]
Metoclopramide	409	3	0.7 [0.2, 2.3]	0.6 [0.2, 2.0]	0.7 [0.2, 2.0]	0.7 [0.2, 2.2]	0.7 [0.2, 2.1]	0.6 [0.2, 2.0]	404	3	0.7 [0.2, 2.3]	0.7 [0.2, 2.1]
Drotaverine	249	7	2.8 [1.3, 6.0]	2.3 [1.1, 5.0]	2.6 [1.2, 5.4]	2.4 [1.1, 5.2]	2.7 [1.3, 5.8]	1.8 [0.8, 3.9]	245	7	2.9 [1.3, 6.1]	2.3 [1.1, 5.0]
Propulsives	442	3	0.7 [0.2, 2.1]	0.6 [0.2, 1.9]	0.6 [0.2, 1.9]	0.6 [0.2, 2.1]	0.6 [0.2, 1.9]	0.6 [0.2, 1.9]	436	3	0.7 [0.2, 2.1]	0.6 [0.2, 2.0]
Insulins and analogues for injection, fast-acting	312	2	0.6 [0.2, 2.5]	0.6 [0.2, 2.4]	0.6 [0.1, 2.3]	0.5 [0.1, 2.2]	0.6 [0.1, 2.4]	0.6 [0.1, 2.3]				
Multivitamins and minerals	1,708	18	1.0 [0.7, 1.7]	1.0 [0.6, 1.7]	0.9 [0.6, 1.5]	1.0 [0.6, 1.6]			1,685	18	1.0 [0.7, 1.7]	1.0 [0.7, 1.7]
Multivitamins and other minerals, incl. combinations	1,612	16	1.0 [0.6, 1.6]	1.0 [0.6, 1.6]	0.9 [0.5, 1.4]	0.9 [0.6, 1.6]			1,590	16	1.0 [0.6, 1.6]	1.0 [0.6, 1.6]
Tocopherol (vitamin E)	42	3	7.6 [2.3, 24.5]	5.7 [1.7, 19.6]	6.8 [2.1, 22]	6.0 [1.7, 21.5]			41	3	7.6 [2.4, 24.8]	5.8 [1.7, 19.9]
Magnesium	552	9	1.6 [0.8, 3.2]	1.4 [0.6, 3.0]	1.5 [0.8, 2.8]	1.4 [0.6, 3.0]			512	9	1.7 [0.9, 3.4]	1.4 [0.6, 3.0]
Enoxaparin	227	3	1.3 [0.4, 4.1]	1.6 [0.5, 5.2]	1.2 [0.4, 3.7]	1.4 [0.4, 4.3]	1.2 [0.4, 3.9]	1.6 [0.5, 5.2]	214	3	1.4 [0.4, 4.3]	1.8 [0.6, 5.5]
Iron bivalent, oral preparations	1209	12	1.0 [0.6, 1.7]	1.1 [0.6, 2.1]	0.9 [0.5, 1.6]	0.9 [0.5, 1.6]			1,172	12	1.0 [0.6, 1.8]	1.2 [0.6, 2.1]
Ferrous sulphate	834	11	1.3 [0.7, 2.4]	1.5 [0.8, 2.7]	1.2 [0.7, 2.1]	1.1 [0.6, 2.0]			808	11	1.3 [0.7, 2.4]	1.5 [0.8, 2.8]
Folic acid	9,981	99	1.0 [0.8, 1.2]	0.9 [0.7, 1.1]	0.9 [0.7, 1.1]	0.9 [0.7, 1.1]			9,800	97	1.0 [0.8, 1.2]	0.9 [0.7, 1.1]
Gynecological antibiotics	234	3	1.3 [0.4, 4.0]	1.5 [0.5, 4.9]	1.1 [0.4, 3.6]	1.1 [0.3, 3.6]	1.2 [0.4, 3.7]	1.2 [0.4, 3.9]	219	3	1.3 [0.4, 4.2]	1.6 [0.5, 5.1]

Imidazole derivatives	377	3	0.8 [0.3, 2.5]	1.0 [0.3, 3.1]	0.7 [0.2, 2.2]	0.9 [0.3, 2.9]	0.7 [0.2, 2.3]	0.7 [0.2, 2.2]	366	3	0.8 [0.3, 2.5]	1.0 [0.3, 3.1]
Isoxsuprine hydrochloride	494	1	0.2 [0.0, 1.4]	0.5 [0.1, 3.8]	0.2 [0.0, 1.3]	0.4 [0.1, 3.1]	0.2 [0.0, 1.3]	0.3 [0.0, 1.9]	486	1	0.2 [0.0, 1.4]	0.5 [0.1, 3.8]
Pregnen (4) derivatives	1,315	7	0.5 [0.3, 1.1]	0.8 [0.4, 1.7]	0.5 [0.2, 1.0]	0.8 [0.4, 1.7]	0.5 [0.2, 1.0]	0.7 [0.3, 1.4]	1,260	7	0.5 [0.3, 1.1]	0.8 [0.4, 1.8]
Progesterone	1,160	6	0.5 [0.2, 1.1]	0.8 [0.4, 1.8]	0.5 [0.2, 1.0]	0.8 [0.3, 1.7]	0.5 [0.2, 1.0]	0.7 [0.3, 1.5]	1,113	6	0.5 [0.2, 1.2]	0.8 [0.4, 1.8]
Dydrogesterone	732	10	1.4 [0.7, 2.5]	1.6 [0.8, 3.0]	1.2 [0.7, 2.3]	1.7 [0.9, 3.2]	1.3 [0.7, 2.4]	1.2 [0.6, 2.3]	722	10	1.4 [0.7, 2.5]	1.6 [0.9, 3.0]
Glucocorticoids	565	2	0.4 [0.1, 1.4]	0.6 [0.1, 2.3]	0.3 [0.1, 1.3]	0.4 [0.1, 1.6]	0.3 [0.1, 1.3]	0.4 [0.1, 1.6]	525	2	0.4 [0.1, 1.5]	0.6 [0.2, 2.4]
Levothyroxine sodium	1,301	7	0.5 [0.3, 1.1]	0.9 [0.4, 1.9]	0.5 [0.2, 1.0]	0.8 [0.4, 1.7]	0.5 [0.2, 1.0]	0.8 [0.4, 1.7]	1,179	7	0.6 [0.3, 1.2]	1.0 [0.5, 2.1]
Amoxicillin and clavulanic acid	370	3	0.8 [0.3, 2.5]	1.0 [0.3, 3.2]	0.7 [0.2, 2.2]	0.9 [0.3, 2.9]	0.7 [0.2, 2.3]	0.7 [0.2, 2.2]	355	3	0.8 [0.3, 2.6]	1.0 [0.3, 3.3]
Penicillins with extended spectrum	1,395	18	1.3 [0.8, 2.1]	1.3 [0.8, 2.1]	1.2 [0.7, 1.8]	1.2 [0.8, 2.0]	1.2 [0.7, 2.0]	1.1 [0.7, 1.8]	1,360	17	1.2 [0.8, 2.0]	1.2 [0.8, 2.0]
Amoxicillin	816	8	1.0 [0.5, 2.0]	1.0 [0.5, 2.1]	0.9 [0.4, 1.8]	1.0 [0.5, 2.0]	0.9 [0.4, 1.8]	0.8 [0.4, 1.6]	799	8	1.0 [0.5, 2.0]	1.0 [0.5, 2.1]
Pivmecillinam	389	9	2.3 [1.2, 4.5]	1.7 [0.8, 3.3]	2.1 [1.1, 4.1]	2.0 [0.9, 4.2]	2.2 [1.1, 4.4]	1.9 [0.9, 3.7]	376	8	2.1 [1.0, 4.3]	1.5 [0.7, 3.2]
Beta-lactamase sensitive penicillins	339	7	2.1 [1.0, 4.4]	1.8 [0.8, 3.8]	1.9 [0.9, 3.9]	1.9 [0.8, 4.1]	2.0 [0.9, 4.2]	1.8 [0.8, 3.9]	328	7	2.1 [1.0, 4.5]	1.9 [0.9, 4.0]
Phenoxymethyl-penicillin	273	4	1.5 [0.5, 3.9]	1.3 [0.5, 3.5]	1.3 [0.5, 3.5]	1.4 [0.5, 4.0]	1.4 [0.5, 3.7]	1.5 [0.5, 4.0]	263	4	1.5 [0.6, 4.0]	1.3 [0.5, 3.7]
Combinations of penicillins, incl. beta-lactamase inhibitors	377	3	0.8 [0.3, 2.5]	1.0 [0.3, 3.2]	0.7 [0.2, 2.2]	0.9 [0.3, 2.9]	0.7 [0.2, 2.3]	0.7 [0.2, 2.2]	362	3	0.8 [0.3, 2.5]	1.0 [0.3, 3.3]
Macrolides	456	1	0.2 [0.0, 1.5]	0.3 [0.0, 1.8]	0.2 [0.0, 1.4]	0.2 [0.0, 1.6]	0.2 [0.0, 1.4]	0.2 [0.0, 1.5]	441	1	0.2 [0.0, 1.6]	0.3 [0.0, 1.8]
Nitrofurantoin	219	4	1.8 [0.7, 4.9]	1.7 [0.6, 4.7]	1.6 [0.6, 4.4]	1.8 [0.6, 4.9]	1.7 [0.6, 4.7]	1.4 [0.5, 3.9]	212	4	1.9 [0.7, 5.0]	1.7 [0.6, 4.8]
Valproate	263	4	1.5 [0.6, 4.1]	1.5 [0.5, 3.9]	1.4 [0.5, 3.7]	1.4 [0.5, 3.8]	1.4 [0.5, 3.8]	1.1 [0.4, 3.0]				
'Other' antiepileptics	188	3	1.6 [0.5, 5.0]	1.2 [0.4, 3.9]	1.4 [0.5, 4.5]	1.1 [0.4, 3.6]	1.5 [0.5, 4.7]	1.1 [0.3, 3.4]				
Benzodiazepine derivatives	394	5	1.3 [0.5, 3.1]	1.6 [0.7, 4.0]	1.1 [0.5, 2.7]	1.6 [0.7, 4.0]	1.2 [0.5, 2.9]	1.3 [0.5, 3.2]	349	5	1.4 [0.6, 3.4]	1.8 [0.7, 4.3]
Diazepam	195	3	1.5 [0.5, 4.8]	1.5 [0.5, 4.8]	1.4 [0.4, 4.3]	1.6 [0.5, 5.0]	1.4 [0.5, 4.5]	1.3 [0.4, 4.0]	175	3	1.7 [0.5, 5.3]	1.6 [0.5, 5.1]
Nasal corticosteroids for topical use	255	3	1.2 [0.4, 3.6]	1.4 [0.4, 4.5]	1.1 [0.3, 3.3]	1.4 [0.4, 4.5]	1.1 [0.4, 3.4]	1.4 [0.4, 4.4]	244	3	1.2 [0.4, 3.8]	1.5 [0.5, 4.7]
Betamethasone	351	2	0.6 [0.1, 2.3]	0.9 [0.2, 3.5]	0.5 [0.1, 2.0]	0.6 [0.1, 2.3]	0.5 [0.1, 2.1]	0.6 [0.2, 2.4]	324	2	0.6 [0.2, 2.4]	0.9 [0.2, 3.7]
Bromhexine	23	3	14.7 [4.4, 49.6]	29.5 [8.2, 105.5]	13.2 [3.9, 44.6]	30.1 [8.3, 108.7]	13.9 [4.1, 47.1]	21.2 [5.9, 75.8]	23	3	14.5 [4.3, 48.9]	29.0 [8.1, 103.8]

Piperazine derivatives	582	2	0.3 [0.1, 1.4]	0.3 [0.1, 1.4]	0.3 [0.1, 1.2]	0.3 [0.1, 1.4]	0.3 [0.1, 1.2]	0.3 [0.1, 1.2]	567	2	0.3 [0.1, 1.4]	0.4 [0.1, 1.4]

Supporting Table 4. Maternal illness signal analysis results - crude and maternal age, registry and time adjusted ORs

	ICD-9	ICD-10	Exposed in dataset	Gastroschisis cases exposed	Crude OR [95% CI]	Adjusted OR [95% CI]
All pregestational Diabetes Mellitus[a]	250	E10-14	882	1	0.1 [0.0, 0.8]	0.1 [0.0, 0.9]
All Diabetes Mellitus (pregestational and gestational)	250, 648.0, 648.8	E10-14, O24	2378	5	0.2 [0.1, 0.5]	0.3 [0.1, 0.8]
Gestational Diabetes Mellitus	648.8	O244	1150	4	0.4 [0.1, 1.0]	0.7 [0.2, 1.8]
Other Endocrine disorders	251-9	E15,E16, E2, E30-5,	223	1		
Mental Disorder	290-9, 300-3, 305-9,310-9	F00-F99	1113	20	1.9 [1.2, 3.0]	1.6 [1.0, 2.4]
Depression	300.4, 311	F32-3	559	13	2.5 [1.5, 4.4]	2.5 [1.5, 4.4]
Mental and behavioural disorders associated with the puerperium		F53	41	3	8.3 [2.6, 27.0]	8.3 [2.6, 27.0]
Chest Cold	466	J20, J21	41	0		
Sore Throat	462, 472.1	J02, J31.2	90	1		
Viral Infection Complicating Pregnancy	647.6, 042, 050-5, 057-079		3	0		
Other Specified Infections (as per Baer et al.[20])	647.3-5, 647.8, 010-018, 084, 056		8	0		
Urinary Tract Infection (UTI)	646.6	O23	1211	13	1.1 [0.7, 2.0]	1.0 [0.5, 1.7]
Genital Herpes	054.1	A60.0	2	0		
Genital Herpes - excluding those taking antiherpetic medication	054.1	A60.0	2	0		
Sexually Transmitted Infection (STI)	090-097, 054.1, 131, 647.0-2	A50-A64, O98.1-3, M02.3	86	5	6.5 [2.6, 16.1]	2.9 [1.1, 7.2]
STI (including thrush)	090-097, 054.1, 131, 647.0-2, 112.1	A50-A64, O98.1-3, M02.3, B37.3	150	6	4.4 [1.9, 10.0]	2.5 [1.1, 5.9]
UTI or STI	646.6, 090-097, 054.1, 131, 647.0-2	O23, A50-A64, O98.1-3, M02.3	1298	18	1.5 [0.9, 2.4]	1.2 [0.7, 1.9]

STI (including thrush) or UTI	646.6, 090-097, 054.1, 131, 647.0-2, 112.1	O23, A50-A64, O98.1-3, M02.3, B37.3	1355	18	1.4 [0.9, 2.3]	1.1 [0.7, 1.8]
STI and UTI	646.6 & 090-097, 054.1, 131, 647.0-2	O23 & A50-A64, O98.1-3, M02.3	1	0		
STI (including thrush) and UTI	646.6 & 090-097, 054.1, 131, 647.0-2, 112.1	O23 & A50-A64, O98.1-3, M02.3, B37.3	6	1		

[a] Includes Norway registry

Supporting Table 5. Maternal illness exploratory analysis results - crude and maternal age, registry and time adjusted ORs

	ICD-9	ICD-10	Exposed in dataset	Gastroschisis cases exposed	Crude OR [95% CI]	Adjusted OR [95% CI]
Asthma[a]	493	J45	21,166	31	1.5 [1.1, 2.2]	1.1 [0.8, 1.6]
Epilepsy[a]	345	G40	974	7	1.1 [0.5, 2.3]	1.0 [0.5, 2.1]
Pre-eclampsia[a]	642.5	O14	817	5	0.6 [0.3, 1.5]	0.5 [0.2, 1.2]
Gastritis and duodenitis	535	K29	101	4	4.4 [1.6, 11.9[	3.1 [1.1, 8.8]
Chronic Interstitial Nephritis	[b]	N11	159	3	2.0 [0.6, 6.4]	1.2 [0.4, 3.8]
Hypothyroidism	243, 244	E00-E03, E89.0	1010	2	0.2 [0.1, 0.8]	0.3 [0.1, 1.2]
Obesity	278	E66	1555	12	0.8 [0.5, 1.4]	0.6 [0.3, 1.0]
Haemorrhage in early pregnancy	640	O20	2028	27	1.4 [1.0, 2.1]	1.5 [1.0, 2.3]
Acute upper respiratory infections of multiple or unspecified sites	465	J06	360	13	4.0 [2.3, 7.0]	2.7 [1.5, 4.8]
Premature rupture of the membranes	658.1	O42	276	5	1.9 [0.8, 4.7]	1.2 [0.4, 3.3]
Influenza	487, 488	J09-J11	705	3	0.5 [0.1, 1.4]	0.9 [0.3, 2.9]
Bacterial Infection of Unspecified Site	[b]	A49	47	3	7.2 [2.2, 23.2]	3.6 [1.1, 12.0]
Hyperemesis	643	O21	371	4	1.2 [0.4, 3.1]	1.0 [0.4, 2.7]
Tonsillitis	463	J03	37	3	9.3 [2.9, 30.3]	8.4 [2.4, 29.3]

[a] Includes Norway registry

[b] ICD-9 and ICD-10 codes not comparable for this diagnosis so analysis was restricted to the ICD-10 code.

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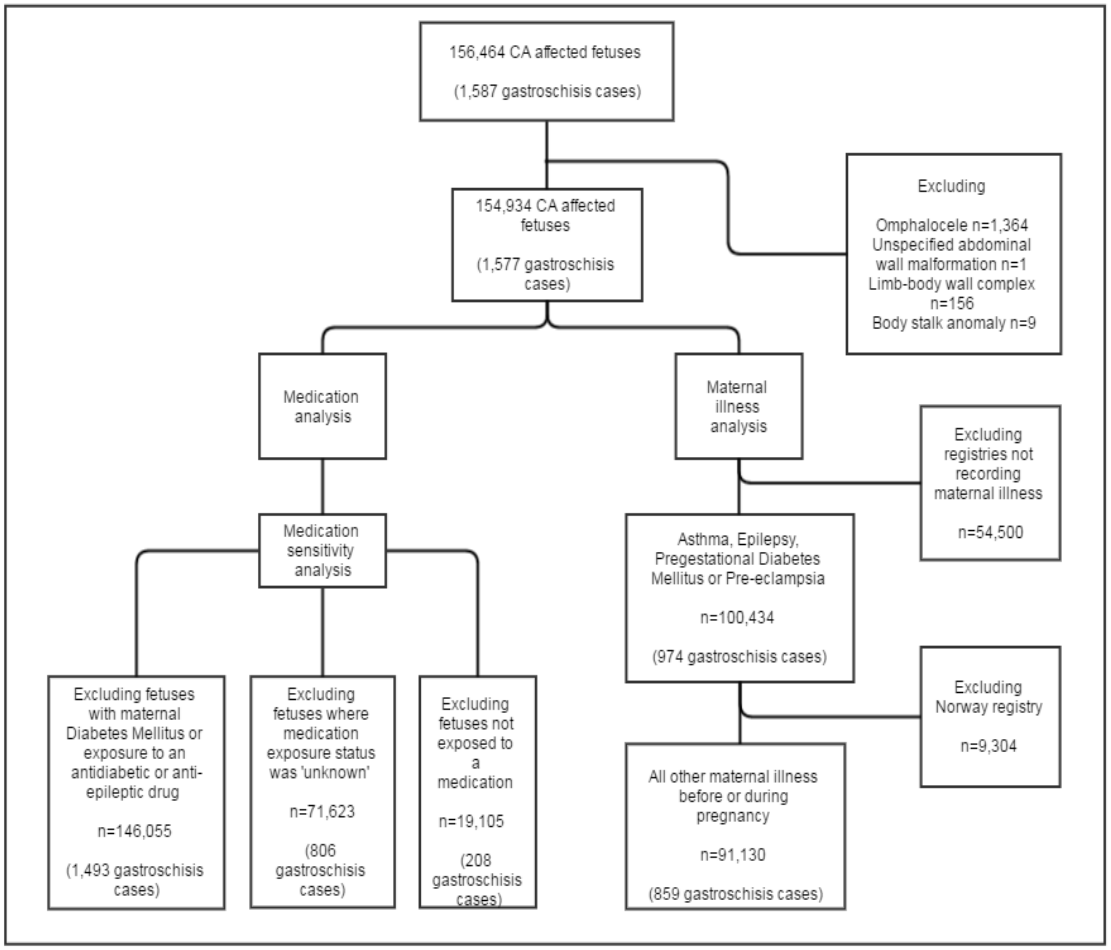
Supporting Figure 1. Flowchart detailing number of congenital anomaly affected foetuses, excluding those with chromosomal/monogenic conditions, included at each stage of the analysis

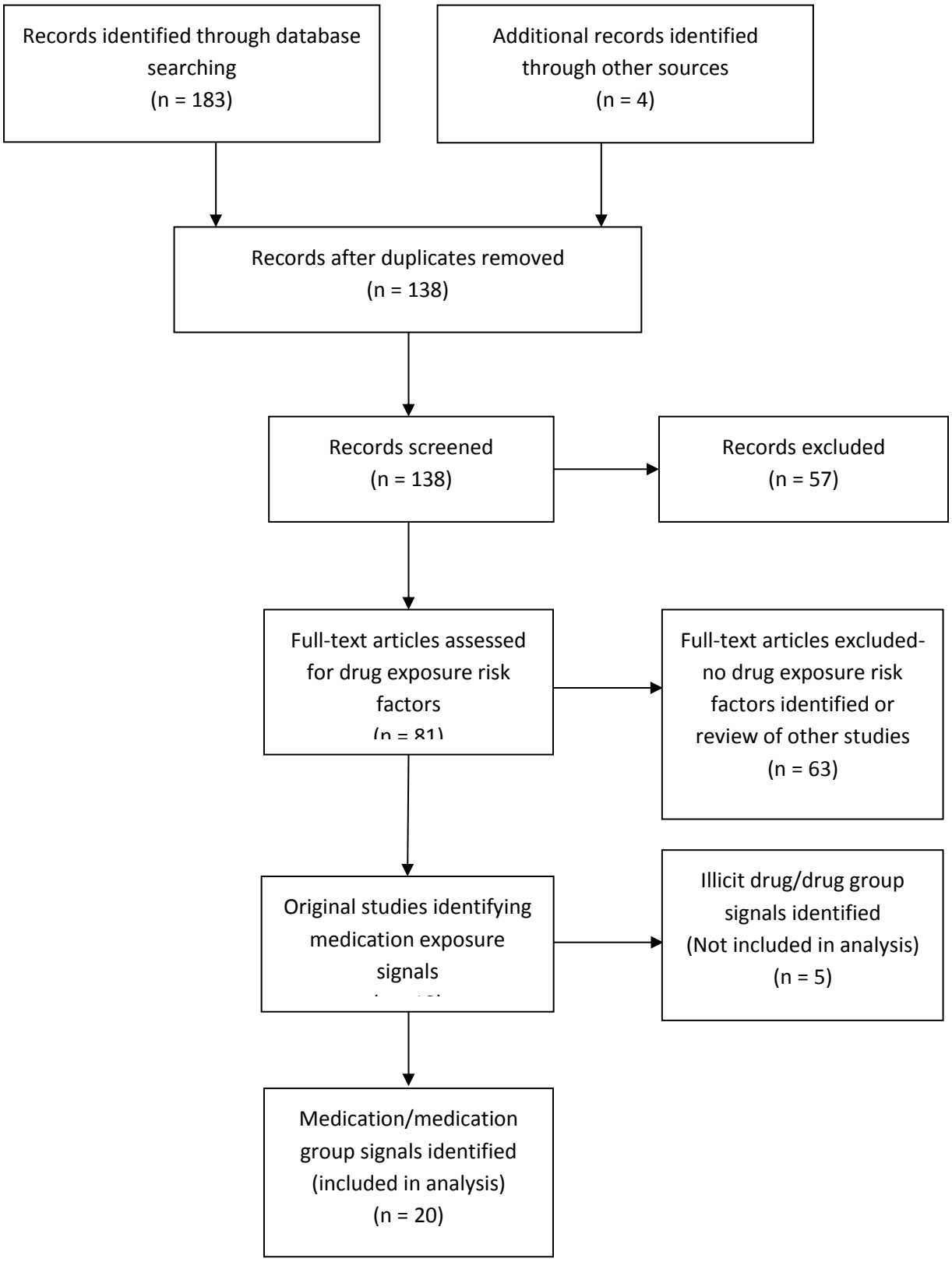


[A] includes those with pregestational diabetes, gestational diabetes or exposure to an antidiabetic medication.

[B] includes only those exposed to a medication, exposed only to vitamin/minerals, or known not to be exposed to a medication.

[C] those exposed only to vitamins/minerals were not considered to be medication exposed.

Supporting figure 2. Flowchart detailing the literature review for first trimester medication exposure signals.



Supporting figure 3. Flowchart detailing the literature review for first trimester maternal illness exposure signals